NEW RESEARCH STRATEGIES IN OSTEOGENESIS IMPERFECTA

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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
(http://www.nih.gov/niams/)
National Institute on Aging (NIA)
(http://www.nih.gov/nia/)
National Institute of Child Health and Human Development (NICHD)
(http://www.nichd.nih.gov/)

Letter of Intent Receipt Date: February 14, 2001
Application Receipt Date: March 14, 2001

THIS RFA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS RFA/PA.

PURPOSE

This initiative is intended to stimulate and support new research projects that have the potential to increase our understanding of skeletal pathology in osteogenesis imperfecta (OI), and to lead to improved therapeutic approaches to the disease. In particular, it is intended that new studies should test the importance of dysregulated bone remodeling in the pathogenesis of OI, with a view to exploiting pharmacological therapies that may ameliorate the consequences of the underlying genetic defects. A second major goal is an improved understanding of osteoprogenitor cell biology that will form the basis for future therapeutic efforts employing genetic modification and transplantation of such cells.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This Request for Applications (RFA), New Research Strategies in Osteogenesis

Imperfecta, is related to the priority areas of fetal, infant and child deaths, and developmental disabilities. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) Research Project Grant (R01) award mechanism. Only new (Type 1) applications will be accepted for this initiative. Competing continuation (Type 2) applications will not be accepted. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this RFA may not exceed 5 years. This RFA is a one-time solicitation. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures. The earliest anticipated award date is September 30, 2001.

Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by the NIH. Complete and detailed instructions and information on Modular Grant applications can be found at http://grants.nih.gov/grants/funding/modular/modular.htm

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. In such a case, a letter of agreement from either the GCRC program director or principal investigator should be included with the application.

FUNDS AVAILABLE

The NIAMS intends to commit up to $1 million in FY 2001 to fund 3 to 5 new grants in response to this RFA. In addition, the NIA and NICHD will consider for funding those meritorious

applications that are relevant to the Institutes' respective missions. An applicant may request a project period of up to 5 years and a budget for direct costs of up to $250,000 per year. Because the nature and scope of the research proposed may vary, it is anticipated that the size of each award will also vary. Although the financial plans of the participating Institutes provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications of interest to each Institute. At this time, it is not known if this RFA will be reissued.

RESEARCH OBJECTIVES

Background

Osteogenesis imperfecta (OI) is a genetic disease of bone, caused by mutations in a gene for type I collagen, the principal structural protein of bone. Depending on the specific mutation, the severity of the disease varies from a mildly increased risk of fracture to perinatal lethality. Severe non-lethal forms cause significant disability, deformity, and chronic pain. A true "cure" of the disease would presumably require correction of the underlying genetic defect. In September of 1999, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the NIH Office of Rare Diseases, the Osteogenesis Imperfecta Foundation, and the Children's Brittle Bone Foundation co-sponsored a meeting of investigators and patient advocates to discuss the implications of recent reports of therapeutic success in treating osteogenesis imperfecta. A report of this meeting is available at http://www.nih.gov/niams/reports/osteogenimperf.htm.

In one reported approach, children with OI were treated with pamidronate, a drug from the bisphosphonate family. Members of this drug group have proven effective in preventing the bone loss and increased fracture risk that occurs in women after menopause. Investigators reported marked improvements in bone mineral density, bone size, fracture incidence, mobility, and pain in children treated with intravenous pamidronate. Although such a pharmacological approach fails to address the underlying cause of OI, the apparent efficacy of the treatment warrants further investigation. In addition, the suggestion of a significant therapeutic effect with administration of a bisphosphonate underscores the gaps in our understanding of OI. Bisphosphonates generally have the effect of reducing rates of bone resorption, and hence, bone turnover. Many forms of OI are associated with elevated bone turnover rates, leading to osteopenia. But it remains unclear how much of the pathology of OI is due to high-turnover osteopenia, and how much to intrinsic matrix defects caused by the collagen mutations. It may be that addressing metabolic imbalances, presumably caused by abnormal bone matrix, can ameliorate many of the consequences of the collagen mutations, even though the mutations remain.

In the second reported approach, children with OI received bone marrow transplants, in an effort to replace mutant bone cells (which arise from precursors in the marrow) with normal cells. Investigators reported that allogeneic bone marrow transplantation in children with OI resulted in increases in growth rate and total body bone mineral content, accompanied by histologic changes indicative of new bone formation, and a decreased incidence of fractures. The inherent risks of the transplantation procedure argue for caution in pursuing this approach. In addition, low levels of donor cell engraftment in such transplants indicate that much remains to be learned about the biology of non-hematopoietic marrow stromal cells and osteogenic precursor cells. Nevertheless, marrow transplantation, especially if followed by "boost" transfers of non-hematopoietic marrow stromal cells from the same donor, closely parallels the process that will ultimately be necessary to achieve true gene therapy for OI.

Specific Objectives

This initiative will support biological studies in areas that have the potential to illuminate the mechanisms of skeletal pathology in OI, to improve existing therapeutic approaches, or to lead to new therapies. Projects with interdisciplinary character, such as collaborations between collagen matrix biochemists and cell biologists, or collaborations between clinicians and basic scientists, are encouraged. Studies may make use of materials derived from human subjects, including patients with OI. However clinical trials are not eligible for support under this initiative. The following examples are illustrative, and are not intended to exclude other types of work that address the objectives stated above.

o Studies of interactions between bone cells and bone matrix, including signaling pathways that may operate between cells and components of the matrix, and the consequences of collagen deficiency or structural alteration of collagen for such signaling.

o Studies of the structural and functional consequences of mutations in the type I collagens, especially mutations known to be important in the pathogenesis of OI.

o Studies of pathogenic mechanisms and the action of bisphosphonates in models of OI, such as transgenic mouse strains expressing mutant type I collagens.

o Studies of the mechanisms determining the commitment of pluripotent precursors to the osteogenic pathway, survival of osteogenic cells, and engraftment of transplanted cells in the bone environment, as these processes apply to therapeutic cell transplantation.

o Development and improvement of techniques for the genetic modification of cells in the osteogenic lineage, including strategies for blocking the expression of dominant-negative gene products.

o Studies of the effects of genetic mosaicism for OI-causing mutations.

o Studies on the effects of aging on bone formation and remodeling in osteogenesis imperfecta, including the effects of aging on bone precursor cells.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm: The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.
This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the Inclusion of Children as Participants in Research Involving Human Subjects that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

LETTER OF INTENT

Prospective applicants are asked to submit, by February 14, 2001, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted. Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review. The letter of intent is to be sent (e-mail, fax, or post) to Dr. Tommy Broadwater at the address listed under INQUIRIES.

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants, with the modifications noted below. These forms are available at most institutional offices of sponsored research and from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: GrantsInfo@nih.gov. The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and Institute staff.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

BUDGET INSTRUCTIONS

Modular Grant applications will request direct costs in $25,000 modules, up to a total direct cost request of $250,000 per year. The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

PHS 398

o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in $25,000 increments up to a maximum of $250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION - Prepare a Modular Grant Budget Narrative page. (See http://grants.nih.gov/grants/funding/modular/modular.htm for sample pages.) At the top of the page, enter the total direct costs requested for each year. This is not a Form page.

o Under Personnel, list all project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest $1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of all personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount. Include the Letter of Intent to establish a consortium.

Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at: http://grants.nih.gov/grants/funding/modular/modular.htm

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.
- List selected peer-reviewed publications, with full citations;

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

The RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

The RFA label available in the PHS 398 (rev. 4/98) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. The sample RFA label available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf has been modified to allow for this change. Please note this is in pdf format. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review.

Submit a signed, typewritten original of the application, including the Checklist, and three signed photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application, and all five sets of any appendix material, must be sent to Dr. Tommy Broadwater at the address listed under INQUIRIES.

Applications must be received by March 14, 2001. If an application is received after that date, it will be returned to the applicant without review.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIAMS. If the application is not responsive to the RFA, CSR staff may contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next review cycle.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAMS in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score. These applications will also receive a second level review by the Advisory Councils of the participating Institutes.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or method?
Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

Schedule

Letter of Intent Receipt Date: February 14, 2001
Application Receipt Date: March 14, 2001
Peer Review Date: June-July, 2001
Council Review: September, 2001
Earliest Anticipated Start Date: September 30, 2001

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o scientific merit (as determined by peer review)
o availability of funds
o programmatic priorities.

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or answer questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

William J. Sharrock, Ph.D.
Musculoskeletal Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Building, Room 5AS-37A
Bethesda, MD 20892-6500
Telephone: (301) 594-5055
FAX: 301-480-4543
Email: ws19h@nih.gov

Jill L. Carrington, Ph.D.
Biology of Aging Program
National Institute on Aging
7201 Wisconsin Avenue, Gateway Building, Room2C231
Bethesda, MD 20892
Telephone: (301) 496-6402
FAX: 301-402-0010
Email: carringtonj@nia.nih.gov

Karen K. Winer, M.D.
Center for Research for Mothers and Children
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 4B11, MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 435-6877
FAX: (301) 480-9791
E-mail: winerk@exchange.nih.gov

Direct inquiries regarding review issues to:

Tommy Broadwater, Ph.D.
Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A25U
Bethesda, MD 20892-6500
Telephone: (301) 594-4953
FAX (301) 480-4543
Email: broadwatert@mail.nih.gov

Direct inquiries regarding fiscal matters to:

Melinda Nelson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A49
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Linda Whipp
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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research, No. 93.866, Aging Research, and No. 93.865, Research for Mothers and Children. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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